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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/067,974	02/08/2002	Lhing-Yew Li		3799

45453 7590 05/01/2006

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EXAMINER	
STEADMAN, DAVID J	
ART UNIT	**PAPER NUMBER**
1656	

DATE MAILED: 05/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/067,974	LI ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 February 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,15-24 and 26-44* is/are pending in the application.

4a) Of the above claim(s) *24 and 40-42* is/are withdrawn from consideration.

5)☒ Claim(s) *44* is/are allowed.

6)☒ Claim(s) *1-13,15-23,26-33,37-39 and 43* is/are rejected.

7)☒ Claim(s) *34-36* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 1-13, 15-24, and 26-44 are pending in the application.

[2] Applicant's amendment to the claims, filed on 2/16/2006, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[3] Applicant's amendment to the specification, filed on 2/16/2006, is acknowledged.

[4] Applicant's arguments filed on 2/16/2006 have been fully considered and are deemed to be persuasive to overcome some of the objections and/or rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[5] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Election/Restriction

[6] Claims 24 and 40-42 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 11/21/2003.

Claim Objection(s)

[7] Claim 4 is objected to in the recitation of "fifth nucleotide molecule…wherein said fifth polynucleotide molecule." It is suggested that applicant maintain consistent use of

terminology and replace "nucleotide" in the term "fifth nucleotide molecule" with "polynucleotide."

[8] Claim 4 is objected to as being grammatically incorrect in the recitation of "an ORF2 polypeptide of SEQ ID NO:10" in line 7 of part (c). Because SEQ ID NO:10 is a specific polypeptide, the claim should read "the ORF2 polypeptide of SEQ ID NO:10."

Claim Rejections - 35 USC § 112, Second Paragraph

[9] The rejection of claim 39 under 35 U.S.C. 112, second paragraph, as being unclear in the recitation of "pDElia2$_{FC5}$-KDB2HL" is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a prior Office action.

RESPONSE TO ARGUMENT: Applicant argues the "pDElia2$_{FC5}$-KDB2HL" construct is described at ¶¶ [0092], [0110], and [0012] of the specification.

Applicant's argument is not found persuasive. The examiner can find no description of a "pDElia2$_{FC5}$-KDB2HL" construct at ¶¶ [0092], [0110], and [0012] of the specification. ¶ [0092] describes methods of inserting a nucleic acid into a host cell chromosome, ¶ [0110] describes construction of a "pDElia2$_{FC5}$-KDB2," and ¶ [0112] teaches construction of a "pDElia2$_{FC5}$-KDB2HP1L" construct. As noted in the prior Office action, the examiner can find no description of a "pDElia2$_{FC5}$-KDB2HL" vector construct. It is suggested that applicants clarify the meaning of a "pDElia2$_{FC5}$-KDB2HL" vector construct.

[10] Claims 4-6, 11, 15, and 29-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites a polynucleotide comprising four separate nucleic acids. Claim 4 (claims 5-6, 11, 15, and 29-30 dependent therefrom), which depends from claim 1, is confusing in the recitation of "a sixth nucleic acid" as it is unclear as to the nucleic acid that is intended as the fifth nucleic acid. While the examiner acknowledges that part (c) of claim 4 recites a "fifth nucleotide molecule," this "fifth nucleotide molecule" is optional and in its absence, it is unclear as to the intended fifth nucleic acid. It is suggested that applicant clarify the meaning of the claims.

Claim Rejections - 35 USC § 112, First Paragraph

[11] The new matter rejection of claims 2-4 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in the prior Office action. The examiner can find no response from applicant addressing the instant rejection. Applicant is reminded that findings of the examiner which are not challenged are usually accepted as fact. See *In re Kunzmann*, 326 F.2d 424, 140 USPQ 235 (CPA 1964).

[12] The new matter rejection of claims 3-4 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in the prior Office action.

RESPONSE TO ARGUMENT: Applicant argues the rejection is inappropriate because it misconstrues the nature of the claims. Applicant argues the ability of the encoded truncated ORF2 polypeptide to increase lysine biosynthesis is "a functional limitation included to identify those variants or truncations of ORF2 that are within the invention and is not a "generic" characteristic of ORF2 truncations that are outside the scope of the claim.

As noted in the prior Office action, applicant fails to show support in the specification for the recited variants or truncations of ORF2 as encompassed by the claims having the ability to increase lysine synthesis. The examiner acknowledges applicant's intent for the limitation to define the scope of ORF2 truncations. However, this is not the issue. The issue is whether the specification provides support for a nucleic acid molecule encoding a truncated variant ORF2 polypeptide as encompassed by the claims wherein said ORF2 polypeptide increases lysine synthesis. As noted in the prior Office action, the examiner can find no support for such a limitation in the original application and applicant is invited to show such support.

[13] The new matter rejection of claim 8 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in the prior Office action.

RESPONSE TO ARGUMENT: Applicant argues support for claim 8 can be found at ¶¶ [0066] and [0112] of the specification.

The examiner acknowledges applicant's cited support for the limitations of claim 8. However, the examiner can find no support for an ask/asd *operon* encoding variant polypeptides as recited in the claims at ¶¶ [0066] and [0112] of the specification. Applicant is invited to show support the recited limitation at issue.

[14] Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

MPEP § 2163 states, "when filing an amendment an applicant should show support in the original disclosure for new or amended claims" and "[i]f the originally filed disclosure does not provide support for each claim limitation, or if an element which applicant describes as essential or critical is not claimed, a new or amended claim must be rejected under 35 U.S.C. 112, para. 1, as lacking adequate written description."

Applicant points to ¶¶ [0068] and [0074] for support for the amendment to claims 1 and 34 and points to ¶ [0074] for support for the amendment to claim 2. The examiner can find no support for the recited limitations of claims 1 and 3-4 at ¶¶ [0068] and [0074] of the specification and can find no support for the recited limitations of claim 2 at ¶ [0074] of the specification.

Applicants are invited to show support for the recited limitations.

[15] The written description rejection of claims 1-13, 15-23, 26-33, and 37-38 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in the prior Office action. New claim 43 is included in the instant rejection. Thus, claims 1-13, 15-23, 26-33, 37-38, and 43 are rejected.

RESPONSE TO ARGUMENT: Applicant argues the claimed genus is well-defined and a skilled artisan would recognize that applicant was in possession of the claimed invention at the time of the invention. Applicant argues the claims define the genus of nucleic acids and amino acid sequences by function and structure and are exemplified in the disclosure of the specification.

Applicants' argument is not found persuasive. While the genus of recited nucleic acids is structurally limited to having the recited identity limitations and functionally limited to encoding polypeptides having ask, asd, dapB, ddh, ORF2, and lysA activity in *Corynebacterium,* the genus remains widely variant with respect to the structures of the encoding nucleic acids and the single representative species of each encoding nucleic acid fails to reflect the variation among the members of the genus. While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus", it is also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus." It was recognized by the Court in *Mycogen Plant Science Inc. v. Monsanto Co.*, 58 USPQ2d 1030 (CAFC 2001) that the arts of chemistry and biology are "unpredictable arts." As such, the disclosure of the

single species of each nucleic acid fails to provide an adequate written description of each genus of encoding nucleic acids.

Given the lack of description of a representative number of polynucleotides, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[16] The scope of enablement rejection of claims 1-13, 15-23, 26-33, and 37-38 are rejected under 35 U.S.C. 112, first paragraph, for the reasons of record and the reasons stated below. The rejection was fully explained in the prior Office action. New claim 43 is included in the rejection. Thus, claims 1-13, 15-23, 26-33, 37-38, and 43 are rejected.

RESPONSE TO ARGUMENT: Applicant argues that analysis of the Factors of *In re Wands* would lead a skilled artisan to conclude the scope of the claimed invention is fully enabled by the specification. Applicant argues the claims are not so broad as stated in the Office action and are instead defined by identity limitations. Applicant argues the high level of skill in the art and the state of the art at the time of the invention weigh in favor of enablement of the claimed invention. Applicant argues that in the vast majority of cases single mutations do not affect polypeptide activity and conservative substitutions are known to be tolerated. Applicant argues that the Office's cited reference (referring to Branden et al., cited in the prior Office action), published eight years prior to the filing of the instant application, cannot be used to support the assertion of unpredictability. Applicant argues the specification provides adequate

direction, guidance, and working examples to make and use the claimed invention without undue experimentation.

Applicants' argument is not found persuasive. While the scope of recited nucleic acids is structurally limited to having the recited identity limitations and functionally limited to encoding polypeptides having ask, asd, dapB, ddh, ORF2, and lysA activity in *Corynebacterium,* the breadth of the each recited nucleic acid encompasses a substantial number of variants, which, the examiner maintains, would require undue experimentation to make. For example, the nucleic acid of part (a) of claim 1 encompasses any nucleic acid that is 90% identical to SEQ ID NO:1 (a 1266 nucleotide sequence) and is 80% identical to SEQ ID NO:2 (a 421 amino acid polypeptide) having ask activity. Due to the variability of codons in the third nucleotide position, the 90% identity to SEQ ID NO:1 limitation is broader that the 80% identity limitation to SEQ ID NO:2 and thus, in the interest of brevity, the examiner will focus only on the 80% identity limitation to SEQ ID NO:2. The 80% identity limitation to SEQ ID NO:2 allows for up to 20% or 84 amino acids, of the amino acids of SEQ ID NO:2 to vary. The reference of Guo et al. (*Proc Natl Acad Sci* 101:9205-9210, 2004) teaches a study suggesting that the percentage of variants having multiple substitutions that maintain activity appears to be exponentially related by the simple formula: $(.66)^x$ x 100% (where x is the number of mutations introduced). As noted above, the claims broadly encompass a polypeptide that can have 84 amino acids of SEQ ID NO:2 altered. Applying the formula of Guo et al., one would expect only $(.66)^{84}$ x 100% or 6.9 x 10^{-14} % of random mutants having 84 simultaneous mutations of SEQ ID NO:2 to be active. Thus, a significant number of

variants must be screened in order to isolate those variants of SEQ ID NO:2 having the desired ask activity. That screening such a substantial number of variants is not routinely practiced in the art is evidenced by Hult et al (*Curr Opin Biotechnol* 14:395-400, 2003), which teaches that recent attempts to randomly obtain variants of a given polypeptide included screening of "6000 transformants" (p. 396, left column, top) or 3.4 x 10^7 variants (p. 396, left column, bottom). In this case, the specification fails to disclose even a single variant of SEQ ID NO:2 and further fails to specific provide guidance for making even a single variant of SEQ ID NO:2 with an expectation that the resulting variant would have the desired activity/utility. The breadth of the claims is substantially increased when one considers that the claims encompass not only nucleic acids encoding variants of SEQ ID NO:2, but also nucleic acids encoding variants of SEQ ID NO:4, 6, 8, 10, and 12.

Applicant argues that a single mutation is not likely to alter polypeptide activity. The examiner agrees with this point. However, as noted above, the claims are not so limited. Applicant further argues that the teachings of Branden et al. are not currently relevant. However, applicant fails to acknowledge the teachings of Witkowski et al. (cited in the previous Office action), which support the teachings of Branden et al. and shows that even as late as 1999 (around the time of the invention), the teachings of Branden et al. are just as true as they were in 1991. Further, it is noted that applicant fails to provide any objective evidence to support the claim that the teachings of Branden et al. were not relevant at the time of the invention.

The examiner maintains the position that in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of non-routine experimentation required, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Double Patenting Rejection(s)

[17] The provisional double patenting rejection of claims 1-13, 15-23, and 26-39 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 19-24 and 27-31 of co-pending application 10/771,695 is maintained for the reasons of record. New claims 43-44 are included in the provisional rejection. Thus claims 1-13, 15-23, 26-39, and 43-44 are provisionally rejected.

RESPONSE TO ARGUMENT: Applicant elects not to file a terminal disclaimer at this time because this is a provisional rejection and both applications continue to undergo prosecution.

Examiner Comment/Clarification

[18] Claim 3, part (a) and claim 4, part (c) recite "ORF2 polypeptide with an amino acid sequence at least 80% identical to SEQ ID NO:10" and claim 3, part (b) recites "ORF2 polypeptide has an amino acid sequence at least 25% identical to SEQ ID NO:10." The examiner has interpreted the term "an amino acid sequence" in accordance with MPEP 2111 as meaning a fragment of as few as two amino acids. Thus, the recited limitation of being "90% identical to SEQ ID NO:9" is the limiting structural characteristic of claim 3, part (a) and claim 4, part (c) and the recited limitation of being "25% identical to SEQ ID NO:9" is the limiting structural characteristic of claim 3, part (b).

Conclusion

[19] Status of the claims:

Claims 1-13, 15-24, and 26-44 are pending.

Claims 24 and 40-42 are withdrawn from consideration.

Claims 1-13, 15-23, 26-33, 37-39, and 43 are rejected.

Claims 34-36 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim 44 is in condition for allowance.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Monday to Friday, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1656